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REVIEW ARTICLE

Bias and small-study effects influence treatment effect estimates: a meta-epidemiological study in oral medicine

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Abstract

Objectives: To examine the influence of the following study characteristics on their study effect estimates: (1) indexing in MEDLINE, (2) language, and (3) design. For randomized trials, (4) trial size and (5) unequal randomization were also assessed.

Study Design and Setting: The CAtegorical Dental and Maxillofacial Outcome Syntheses meta-epidemiologic study was conducted. Eight databases/registers were searched up to September 2012 for meta-analyses of binary outcomes with at least five studies in the field of dental and maxillofacial medicine. The previously mentioned five study characteristics were investigated. The ratio of odds ratios (ROR) according to each characteristic was calculated with random-effects meta-regression and then pooled across meta-analyses.

Results: A total of 281 meta-analyses were identified and used to assess the influence of the following factors: non-MEDLINE indexing vs. MEDLINE indexing ($n = 78$; ROR, 1.12; 95% confidence interval [CI]: 1.05, 1.19; $P = 0.001$), language ($n = 61$; $P = 0.546$), design ($n = 24$; $P = 0.576$), small trials (<200 patients) vs. large trials (≥ 200 patients) ($n = 80$; ROR, 0.92; 95% CI: 0.87, 0.98; $P = 0.009$) and unequal randomization ($n = 36$; $P = 0.828$).

Conclusion: Studies indexed in MEDLINE might present greater effects than non-indexed ones. Small randomized trials might present greater effects than large ones. © 2014 Elsevier Inc. All rights reserved.

Keywords: Dentistry; Meta-analysis; Systematic review; Effect size; Meta-epidemiologic study; systematic error

1. Introduction

In the evidence-based concept, systematic reviews and meta-analyses of randomized clinical trials provide the best available evidence of medical interventions. Empirical evidence indicates that flaws in the design, conduct, and analysis of trials can lead to bias and distort their effects. Previous meta-epidemiologic studies have assessed the influence of various study characteristics on their effects, including among others indexing in MEDLINE [1], language [2,3], design [4,5], methodological characteristics [6], sample size [7−10], and others with most focus on randomized trials.

The concept of evidence-based decision-making in dentistry started to gain popularity in the mid-90s and is rapidly expanding. However, several issues still exist in this research field. Data are, for example, often complex or clustered with the patient, mouth quadrant, jaw, tooth, or even tooth surface serving as the unit of analysis. In some instances, ''dental research'' remains isolated from medical research or focuses on surrogate end points [11]. Moreover, key aspects of interventional clinical studies such as randomization or blinding are often impossible or only partly possible (as the patient is aware of the intervention) and even when possible, their conduct is problematic [12,13]. In the field of orthodontics, for example, meta-analyses of randomized trials are just the 23% of all existing meta-analyses [14]. However, one must also bear in mind that systematic differences exist between interventional studies, where randomization can be and is applied,

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What is new?

Key findings

- Confirmation that studies indexed in MEDLINE might present more beneficial effects than studies non-indexed in MEDLINE.
- Confirmation that small randomized trials (<200 patients) might present more beneficial effects than large randomized trials (≥200 patients).
- Unequal randomization in randomized controlled trials might not necessarily be associated with observed effects.

What this study adds to what was known?

- There was no evidence of larger treatment effects in trials with unequal randomization.

What is the implication and what should change now?

- Systematic reviews in oral and maxillofacial medicine need to include several databases in their literature search, apart from MEDLINE
- Systematic reviews that include only small randomized trials might be more prone to bias than systematic review that include both small and large randomized trials.

and observational studies, where randomization is not applicable or possible.

In most randomized study designs, patients are allocated by protocol to equally sized groups with the ratio 1:1 being most used for reasons of practicality, cost-effectiveness, or statistical reasons. Unequal randomization, in most cases, favors the experimental arm and might even have ethical advantages over balanced designs in some cases [15], and the loss of power is small with allocation ratios of up to 2:1 [16]. Often, however, a larger sample size is required to counterbalance the loss of power. When, however, we talk about unequal randomized groups, one must discriminate between study design by protocol and study realization. Small discrepancies in group sizes are due to differential attrition or random chance (ie, study realization). Greater discrepancies may result from unequal randomization schemes (ie, design according to protocol) [17,18]. Large discrepancies in group sizes not explained by chance or other reasons by the trialists should be viewed with caution [19–21]. To our knowledge, no study has yet assessed if unequal randomization is associated with effect overestimation or underestimation.

We performed a large-scale assessment of meta-analyses in the field of dental/maxillofacial medicine. We named it the CADMOS study (CAtegorical Dental and Maxillofacial Outcome Syntheses) after *Κάδμος*, the Phoenician prince who sowed the dragon's teeth in the ground and from which fierce warriors sprang. In this first report, we planned to replicate already published empirical evidence about the trials' MEDLINE indexing, language, design, and size with dental meta-analyses. Additionally, we planned to identify whether unequal randomization in a randomized trial might influence the estimated effects.

2. Methods

The protocol for this study was made a priori, based on existing guidelines for systematic reviews [22,23] and previous studies.

2.1. Selection of meta-analyses and component studies

We searched systematically in eight general, open-access, regional, or grey literature databases from inception to September 2012 (Appendix A at www.jclinepi.com) for systematic reviews in the field of oral medicine. Manual literature updates were performed regularly up to March 2013. There were no language, publication year, or publication status restrictions. Translations of articles were arranged where necessary. We contacted 20 area experts to identify missed reviews. We saved the results in RefWorks (Bethesda, MD, USA) and exported them in pre-defined forms. For this study, eligible were (1) review articles in any field of dentistry with at least one meta-analysis of binary outcomes, (2) with at least five included primary studies (as they are more robust to the effects of removing one or two studies [24] and for the calculation of between-study heterogeneity [22]), which (3) reported raw data or estimated odds ratios for the component studies.

The titles and abstracts of all obtained reports were screened by one author (S.N.P.). Then three authors (S.N.P., G.A., and E.T.) evaluated the full reports of meta-analyses for eligibility using pre-defined and piloted forms. Eligible reviews were divided in six dental specialties: endodontics, oral and maxillofacial surgery/medicine, orthodontics and dentofacial orthopedics, pedodontics, periodontics, and prosthodontics. Reports that did not fit in any of those categories made a seventh category named general dentistry. We searched MEDLINE through PubMed to assign unique identifiers to each meta-analysis and each trial. References not indexed were searched in two other databases (Embase and Web of Knowledge) or manually assigned a unique identifier. Using the identifier, we found overlaps and then removed duplicate meta-analyses or trials until there was no actual overlap of the same data between the remaining meta-analyses. Duplicate trials included in two or more meta-analyses were removed from the meta-analysis with the greater number of included studies (or randomly in case of a tie) until no overlap existed.

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